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A PROSPECTIVE COMPARATIVE STUDY TO EVALUATE THE EFFICACY AND TOLERABILITY OF SERTRALINE WITH METHYLCOBALIN AND PREGABALIN WITH METHYLCOBALIN IN THE TREATMENT OF DIABETIC NEUROPATHIC PAIN

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ABSTRACT

Different classes of medications like tricycle antidepressants, anticonvulsants, serotonin and norepinephrine reuptake inhibitors, opioids are used in the management of diabetic peripheral neuropathic pain. The studies on sertraline as an alternative to the above drugs are very minimal, hence an effort was made to compare with pregabalin. The aim of the study was to evaluate the efficacy and tolerability of two combinations (sertraline with methylcobalin and pregabalin with methylcobalin) in the treatment of diabetic peripheral neuropathy. This is a prospective, comparative single blind trial conducted in a tertiary care hospital and 100 patients were provided with above two combinations with 50 patients in each group. The primary efficacy endpoint was change in the mean pain score based on neuropathic pain scale. The secondary end points included Michigan neuropathy screening instrument. Routine local and systemic examination was done with the recording of adverse events. Relevant laboratory investigations were also recorded. Sertraline and methylcobalin were matched with pregabalin and methylcobalin in all the characteristics like demographic details and pain scoring scale. As far as the primary outcome was concerned, there was marked improvement in the pain relief, especially sharp pain, dull pain and cold pain seen in pregabalin group. Also a considerable improvement in symptomatology was noted in sertraline group. Thus, this study promised a hope for sertraline a SSRI in the treatment of diabetic peripheral neuropathy as a third choice if the other classes of drugs failed. To conclude, multiple studies have demonstrated the efficacy and safety of pregabalin with methylcobalin group. However, the rationale of combining sertraline with methylcobalin was tried in this study.

KEYWORDS: **Diabetic peripheral neuropathy, sertraline, pregabalin, neuropathic pain scale**

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is defined as the presence of signs and symptoms of peripheral nerve dysfunction in people with diabetes when other causes have been excluded. It occurs due to untreated hyperglycaemia for a prolonged period, along with dyslipidaemia, insulin resistance, autoimmune disorders which damage the nerves. The etiology of DPN is probably unknown may be due to activation of polyol sorbitol pathway, Schwann cell damage, activation of nuclear enzyme ADP-ribose, PARP, myo-inositol depletion. [1-2] The burden of the disease keeps on pacing due to unawareness of the complications, low socioeconomic status, and poor education status. An NCD risk factor conducted throughout India reported that the prevalence of self reported Diabetes is 7.3% in urban followed by 3.1% in rural areas. [3] A population based study done by Chennai Urban, Rural Epidemiology Study (CURES) group reported an incidence of neuropathy to be around 26.1%. [4]Pregabalin, a GABA derivative used in the treatment of seizure disorder, possesses analgesic with anxiolytic activities. The European Federation of Neurological societies pregabalin as a first line agent for the treatment of pain associated with diabetic neuropathy, post-herpetic neuralgia, central neuropathic pain, trigeminal neuralgia and migraine. [5]Methylcobalamin also known as mecobalmin, a vitamin B12 is used in the treatment of peripheral neuropathy and diabetic neuropathy. Vitamin B12 malabsorption is a complication of metformin therapy, which present as the irreversible neuronal damage. Hence, methylcobalin is added in both the study groups. [6]DPN is one of the most common causes of non traumatic amputation. The Mayo clinic suggests pregabalin will be the first choice for diabetic neuropathy following duloxetine which have also secured FDA approval. Sertraline a selective serotonin reuptake inhibitor is prescribed for major depressive disorder, obsessive compulsive disorder, panic disorder. The literature review proved that, sertraline apart from the above indications can be used in the neuropathic pain.[7] The usage of sertraline show some promises but the data is limited. Theoretically, it is believed that the potentiation of serotonergic and noradrenergic activity with the blockade of serotonergic reuptake in particular, if found to have a beneficial effect in neuropathic pain. Hence, a comparative study was put forward to find the efficacy of sertraline with methylcobalin and pregabalin with methylcobalin in a tertiary care teaching hospital, Salem.Aim of our study is to compare the efficacy and tolerability of sertraline with methylcobalin and pregabalin with methylcobalin in Type II Diabetic patients with peripheral neuropathy.

METERIALS AND METHODS

A prospective , single blind , comparative study was conducted among Type II diabetic patients attending the Diabetic Clinic, Department of Medicine, at a tertiary care hospital, VMKVMC, Salem for a period of 6 months between November 2015 and April 2016. The study protocol was submitted to the Institutional Ethics Committee and approval was granted by the same . [IEC No-VMKVMC/IEC/16/04].The screening procedure was done by a diabetologist. Those subjects who were willing to give the informed consent and fulfilling the inclusion criteria were assigned for the study. Patients of either sex, aged 18-80 years with a history of diabetes mellitus with signs of peripheral neuropathy were included in the study. Those patients with diabetic foot, neuropathic ulcer and abnormal liver and kidney function were excluded. Baseline evaluations were performed in all the patients prior to administration of the first dose of the study drug. Patients were explained about the study protocol, including the study visit schedule, frequency of dosage administration, benefits and adverse effects of the study medications. A sample of 100 patients with established diabetic peripheral neuropathy and either type 1 or type 2 diabetes were recruited for the study. Patients were divided into two groups and Group 1patients were given methylcobalin 1500 µg once daily with sertraline 50mg twice daily and Group II were given methylcobalin 1500 µg once daily with pregabalin 50mg thrice daily for a period of 12 weeks. The data were collected with the help of predesigned patient data entry form. Safety and tolerability of the study groups was also recorded. Confidentiality and anonymity of the patient's information were maintained during and after the study period. Fasting blood sugar(FBS), Postprandial blood sugar(PPBS), plasma lipid concentration, HbA1c level were recorded at the beginning and 12th week of the treatment period. Pain and sensory symptoms were measured by using Neuropathy pain scale. [8] Sensory perceptions were assessed by monofilament sensation, vibration perception and ankle reflex as the part of the Michigan neuropathy screening Instrument. Physical assessment and pin prick and touch pressure were assessed as the part of the neuropathy impairment score.

EFFICACY ASSESSMENT

Primary efficacy variable

The primary efficacy variable was an improvement in mean pain score and sensory symptoms and measured by Neuropathy pain scale at baseline and at the end of 12th week.

Secondary efficacy variable

Michigan neuropathy screening instrument was utilized to assess the appearance of feet, any ulceration, ankle reflexes, vibration perception at great toe and monofilament test. The recordings were entered in the predesigned proforma.

Safety assessments

Safety assessments were recorded at the end of each visit along with adverse reactions. Clinically significant changes in symptoms, abnormal laboratory results and untoward reactions were considered to be an adverse effect.

STATISTICAL METHODS

Data were tabulated and statistical analysis was done by using Epi info software. Results were expressed as

frequencies and percentages and Chi-square test was used to compare the demographic data and basic laboratory parameters of the study population. Neuropathic pain score was analyzed at baseline and 12th week by using Student's t-test and comparison of means between the two groups were analyzed by using ANOVA. P value of <0.05 was considered as statistically significant.

RESULTS

Table 1
Age and sex wise distribution of the study population

Age group in years	Group I (n=50)		Group II (n=50)		P value
	Male	Female	Male	Female	
20 – 30	5(10%)	3(6%)	4(8%)	2(4%)	
31 – 40	11(22%0	4(8%)	13(26%)	5(10%)	
41 – 50	6(12%)	2(4%)	2(4%)	3(6%)	
51 – 60	14(32%)	2(6%)	13((26%)	4(8%)	0.4
>60	1(2%)	2(4%)	2(4%)	2(4%)	
Total	37 (74%)	13 (26%)	34 (68%)	16 (32%)	
Mean age	48.2±1.2		49.8±4.2		

P- value derived by applying chi-square test: Table-1 showed the age and sexwise distribution in both the groups About 74% were males in group I and 68% were males in group II with the male: female ratio being 2:1. The mean age was 48.2 in sertraline group and 49.8 years in pregabalin group. Majority of the patient were in the age group of 41 to 60 years. No statistical significance was found between these groups.

Table 2
Socio demographic data of the study population

S.NO	Parameters	Group-I	Group-II
1.	Co-morbidity 1.Hypertension 2.Asthma 3.COPD	No of cases (%) 15(30%) 4(8%) 4(8%)	No of cases (%) 17(34%) 5(10%) 3(6%)
2.	Social habits 1.Smokers 2.Alcoholics 3.Both	No of cases (%) 13(26%) 3(6%) 16(32%)	No of cases (%) 7(34%) 11(22%) 12(24%)
3.	Duration of DPN Duration of diabetes	4.08yrs±4.6 11.5yrs±2.6	3.87yrs±3.16 10.2yrs± 3.7

Table -2 showed the sociodemographic data of both groups. Regarding the comorbidity status 30% of patients were hypertensive, 8% with bronchial asthma , 8% with chronic obstructive pulmonary disease (COPD) in (sertraline) groupI and 34% were hypertensive, 10% had bronchial asthma and 6% had COPD in (pregabalin) groupII. The percentage of alcoholics and smokers among the population was mentioned in Table 2 where DPN is closely associated with the smokers than non-smokers. This data correlate with degree of illness.The average duration of diabetes was 11.5 years in group I and 10.2years in group II. The duration of the symptoms of diabetic peripheral neuropathy was 4.08 years in group I when compared to 3.87 years in group II.

Table 3
Blood sugar level and lipid profile of Group I and Group II patients.

S. No		Group-I Mean	SD	Group-II Mean	SD	P-Value
1.Blood sugar level	FBS PPBS HbA1C	148[2.52] 214[2.64.]	1.05 0.94	106[1.22] 188[1.78]	0.54 0.64	0.74 0.78
2.Lipid profile	LDL HDL TG Total cholesterol	94[1.74] 42[2.22] 165[2.26] 200[2.96]	0.72 0.86 0.7 0.83	118[2.90] 42[2.18] 150[2.0] 174[2.78]	0.22 0.87 0.85 0.73	0.89 0.69 0.97 0.91

P- value derived by applying chi-square test:

Table -3 showed the blood sugar level and lipid profile in both groups. The baseline readings with the mean FBS was 148mg/dl in group I and 106mg/dl in group II. Subsequently the mean PPBS were 214mg/dl in groupI and 188mg/dl in group II. The above table showed lipid profile readings at the start of the study. With the use of statins there was a marked improvement in the lipid profile status of the study subjects.Regarding the pain distribution 90% involvement was noticed in lower extremities when compared to upper extremities. The common symptom noticed in our study subjects was numbness (60%) followed by aching pain (22%), pin pricking (10%) and burning pain (2%).

Table 4

Through the Michigan Neuropathy Screening Instrument, the following values were obtained.

Parameters	Group I(Before Treatment)	GroupI(after treatment)	GroupII(Before treatment)	Group II(After treatment)
1.Appearance of foot	Normal - 28 Dry skin - 8 Infection – 14	Normal -32 Dry skin - 7 Infection -11	Normal -42 Dry skin - 8	Normal – 44 Dry skin - 6
2.Foot ulceration	Normal -48 Ulceration – 2	Normal -50 Ulceration -0	Normal -50	Normal -50
3.Ankle reflex	Normal -50	Normal -50	Normal -50	Normal -50
4.Vibration perception at great toe	Normal -34 Decreased-16	Normal -39 Decreased -11	Normal -32 Decreased-18	Normal -41 Decreased -9
5.Monofilament	Normal -38 Decreased-12	Normal -36 Decreased -14	Normal -36 Decreased-14	Normal -44 Decreased-6

Dry skin and infection was noticed in the groups and reduced after 3 months due to the administration of appropriate antibiotics and emollients. Similarly ulceration was noted in two patients, which responds to antibiotics. Ankle reflexes were normal in all the patients. Vibration perception at great toe is decreased in both the pre-treated patients, but an improvement is noted more in pregabalin than sertraline. Regarding the monofilament test there is a marginal improvement in the sensation in pregabalin group over sertraline group.Table-5 listed the neuropathic scale scores with involvement of 10 categories of pain. Analysis was done by proper scoring before the start of the treatment and after 12 weeks in both the groups.

Table 5

Neuropathic pain scale

Parameters	Group I (sertraline+met) Mean ±SD	Group I(pregabalin+met) Mean± SD	Pvalue(by applying ANOVA)
1.Pain intensity			
Baseline	6.2 ± 0.73	5.6 ± 0.79	0. 79
12th week	5.16± 0.87	1.38± 0.53	0.41
Pvalue(byapplying Student's t- Test)	<0.001	0.04	
2.Sharp pain			
Baseline	5.84± 0.55	5.66 ± 0.91	0.85
12th week	4.10 ± 0.46	2.38 ± 0.67	0.01
P-value	0.22	0.02	
3.Hot pain			
Baseline	5.5 ± 0.50	4.18 ± 1.2	0.65
12th week	3.86± 0.45	2.12 ± 0.89	0.57
P-value	0.002	<0.001	
4.Dull pain			
Baseline	5.32 ± 0.71	5.44± 0.34	0.38
12th week	3.72 ± 0.49	1.42± 0.92	0.05
P-value	<0.001	<0.001	
5.Cold pain			
Baseline	5.26± 0.66	3.92 ± 1.04	0.29
12th week	3.66± 0.56	1.54± 0.65	0.003
P-value	0.002	<0.001	

P value <0.05 is considered as statistically significant.

There is an improvement in pain intensity from the baseline to 12th week with mean baseline value is 6.2 and 5.6 in group I and group II respectively and the mean value at the end of treatment is 5.16 and 1.38 in both groups respectively. There is a statistical improvement in pain relief especially sharp pain, dull pain and cold pain in both the groups with a marginal improvement in pregabalin treated patients when compared to sertraline treated patients.Regarding the intensity of hot pain, there is a statistical improvement in pain relief in both the group after the treatment negligible difference was shown between two groups.

Table 9
Adverse drug reactions among the two groups of patients

Parameters	Group I (n=50)	Group II (n=50)
Adverse events	**Total number of patients = 7 (14%)**	**Total number of patients = 11(22%)**
1.Weight gain	3 (6%)	0
2.Giddiness	1(2%)	3(6%)
3.Dizziness	1(2%)	2 (4%)
4.Sedation	0	1(2%)
5.Drowsiness	2(4%)	3(6%)
6.Peripheral oedema	0	2 (4%)

The adverse effect profile is mild in both groups. Weight gain and drowsiness are more in sertraline Group while giddiness, dizziness and drowsiness are seen in pregabalin group.

DISCUSSION

Diabetes is most common disorder of metabolism and the prevalence keeps on increasing worldwide. Despite the tremendous burden of the disease, there is a lack of structured treatment principles to prevent the complications. Without creating an awareness programme among the general population and diseased persons the complications will be increasing in pace. This is in coherence with Guariguata et al, where an increase in obesity, junk foods, limitation of exercise, Type A personalities will drive the prevalence of disease and the complications. [9]The estimate confirms the diabetic burden across the various regions in the world and India. The changes in urbanization, stress driven life, even in rural areas decreases the expectancy of life and worsening of the diabetic complications especially diabetic neuropathy. In our study, the age specific prevalence of diabetes is in middle age group with males are predominant over females. Smoking and alcohol are the worst risk factors in our study which worsens the DPN. Nutritional interventions, physical activity and weight control programmes remain the cornerstone in preventing complication. Despite the clear guidelines in the screening of at risk population, full effort is not translated in our clinical practice. A single measure of HbA1C gives to a low positive predictive value if the glucose concentration rises abruptly. Hence 2 or more values give a positive predictive value.There is a male predominant in the study in both treatment groups which is similar to other Indian Trials. [10] Boutassira D, Lanteri Minet M showed that neuropathic pain is associated with psychological burden. [11] Hence, patients treated with sertraline have showed a positive response as many studies favour that antidepressants may be administered if the regular medications failed. As far as co- morbid diseases is concerned both the groups were affected with 15% treated with antihypertensive, 4% treated with antiasthma tics and 3% with COPD which is less compared with Elbert S. Huang et al and Mitche et al.[12]Our study had shown a consistent pain relief in the neuropathic pain like sharp pain, dull pain and cold pain in both the treatment groups but a better outcome was noted from pregabalin treated than sertraline group individuals. This is coherent with PRECISE trial which was last updated in 2016. A Cochrane systematic review of various studies showed pregabalin is more efficacious in the treatment of neuropathic pain. [13]Our study population showed a better efficacy in pain relief in both the groups. The pregabalin treated subjects had a greater impact than sertraline group which is similar to 4 clinical trials. [14]This study also explains the pain distribution with 90% involvement in lower extremities with numbness followed by aching pain, pin pricking and burning pain.Even though FDA has not approved sertraline in the treatment of neuropathic pain, our study has shown positive impact in reducing the intensity of various types of DPN. Lee VC, Chen pp suggested that SSRI's can be considered in the treatment of neuropathic pain if the traditional drugs fail. [15] The mechanism behind the action is serotonin together with endogenous opioids modulates the activity in the nociceptive pathway at the dorsal horn of the spinal cord and in the central nervous system. All the 100 patients were given a low dose 1.25mg of Ramipril routinely which leads to a substantial improvement of neuronal blood flow and the improvement in the nerve conduction velocities.

CONCLUSION

Pregabalin, the 1st line drug had showed a positive impact in the management of DPN. But also sertraline showed a promising alternative as third line of treatment. Randomized controlled trials are the only legitimate evidence for the effect of antidepressants in DPN. Hence, randomized controlled trial has to be carried in various centres throughout the world.Inferiority would be declared if the mean improvement for pregabalin was no worse than mean improvement for sertraline.

Recommendations

As per Research Society for the Study of Diabetes in India (RSSDI) 2015 in case of patients with DPN the following factors has to be kept in mind.

1) Manage by stabilizing glucose control and treatment with tricyclic antidepressants. If it fails, switchover to pregabalin/gabapentin and duloxetine then tramadol and oxycodone.

2) Do aware of psychological impact of continuing symptoms , use antidepressants.

3) To agree a foot care plan based on the finding of annual foot review.

4) Risk assessment and classification would be as for recommended care but with sensory assessment done by 10gram monofilament or tuning fork with or without nontraumatic disposable pinprick and peripheral circulation assessment by palpation of pedal pulses.

Limitations

Our study has limitations, prospective study with small sample size, treatment duration is limited to 6months, maximum doses of the drug are not tested in the study population and nerve conduction studies are not preformed.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest.

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